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Review

Mitochondrial dysfunction in Parkinson's disease

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ABSTRACT

Mitochondria are highly dynamic organelles which fulfill a plethora of functions. In addition to their prominent role in energy metabolism, mitochondria are intimately involved in various key cellular processes, such as the regulation of calcium homeostasis, stress response and cell death pathways. Thus, it is not surprising that an impairment of mitochondrial function results in cellular damage and is linked to aging and neurodegeneration. Many lines of evidence suggest that mitochondrial dysfunction plays a central role in the pathogenesis of Parkinson's disease (PD), starting in the early 1980s with the observation that an inhibitor of complex I of the electron transport chain can induce parkinsonism. Remarkably, recent research indicated that several PD-associated genes interface with pathways regulating mitochondrial function, morphology, and dynamics. In fact, sporadic and familial PD seem to converge at the level of mitochondrial integrity.

1. Introduction

Parkinson's disease (PD), the most common movement disorder and the second most common neurodegenerative disease after Alzheimer's disease, is characterized primarily by the loss of dopaminergic neurons in the substantia nigra pars compacta leading to a dopamine deficit in the striatum. The consequent dysregulation of basal ganglia circuitries accounts for the most prominent motor symptoms, including bradykinesia, hypokinesia, rigidity, resting tremor and postural instability. In addition to the typical motor symptoms, various non-motor features may develop, such as autonomic dysfunction, sleep disturbances, depression and cognitive impairment, indicating a more widespread degenerative process. A pathological hallmark of sporadic PD is the presence of proteinaceous deposits within neuronal perykarya (Lewy bodies) and processes (Lewy neurites), mainly composed of α-synuclein, ubiquitin, neurofilaments and molecular chaperones [1]. The role of Lewy bodies in the disease process and their status as a pathognomonic marker of PD is still a matter of discussion. Notably, Lewy bodies are not a consistent finding in familial forms of PD, therefore it has been proposed to classify genetic cases as parkinsonism [2].

Little is known about the etiopathogenesis of PD. The most common sporadic form of PD seems to be a complex multifactorial disorder with variable contributions of environmental factors and genetic susceptibility. Aging is the most important risk factor, thus with increasing average life expectancy the incidence and prevalence of PD will rise considerably in the next future. A major breakthrough in PD research was the identification of genes which are responsible for monogenic familial forms. Mutations in the genes encoding α-synuclein and LRRK2 (leucine-rich repeat kinase 2) are responsible for autosomal dominant forms of PD, presumably by a gain-of-function mechanism. Loss-of-function mutations in the genes encoding parkin, PINK1, and DJ-1 mediate autosomal recessive PD. Sporadic and monogenic forms share important clinical, pathological and biochemical features, notably the progressive demise of dopaminergic neurons in the substantia nigra. Therefore, insight into the function and dysfunction of PD-associated gene products can help to elucidate the underlying mechanisms leading to neuronal cell death. Accumulating evidence indicates that PD-associated genes directly or indirectly impinge on mitochondrial integrity, thereby providing a link to pathopysiological alterations observed in sporadic PD (rev. also in refs. [3–10]). In the following we provide a synopsis of the current knowledge about the role of mitochondria in sporadic PD and familial parkinsonism.

1.1. Sporadic PD and mitochondria

1.1.1. Complex I deficiency

1.1.1.1. Lessons from an illicit drug. In the late 1970s/early 1980s young drug addicts in the United States developed progressive and irreversible parkinsonism after using an illicit drug intravenously. The neurotoxic compound was traced back to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a by-product generated accidentally during the synthesis of a meperidine analog [11,12]. One of these patients, a chemistry graduate student who died of a drug overdose 2

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years after the onset of parkinsonian symptoms, displayed degeneration of the substantia nigra pars compacta without a clear evidence for the presence of Lewy bodies [12]. These findings were confirmed when three more patients came to autopsy 3–16 years after MPTP intoxication [13]. A PD-specific pattern of nigrostriatal degeneration without typical Lewy body pathology has also been observed in non-human primates treated with MPTP [14–17]. Importantly, both the beneficial and long-term adverse effects of L-dopa therapy in MPTP-intoxicated patients/non-human primates are comparable to those in patients suffering from sporadic PD. The neuropathological and clinical similarities between MPTP-induced parkinsonism and sporadic PD promoted the employment of the MPTP monkey model for neuropathological, neurophysiological and preclinical therapeutical studies (rev. in ref. [18]). For reasons of practicability, the MPTP model has also been established in mice, which is now widely used to study some aspects of PD (see refs. [18–24] for detailed reviews on PD animal models).

In parallel to neuropathological studies in MPTP-treated animals, considerable efforts have been made to understand the molecular mechanism of MPTP-induced neurotoxicity. It turned out that MPTP crosses the blood–brain barrier by virtue of its high lipophilicity and is oxidized to a pyridinium species by monoamine oxidase (MAO) B in glial cells [25,26]. This species is further oxidized to the toxic molecule MPP^+, which is released by an unknown mechanism and can be taken up into dopaminergic neurons via the dopamine transporter [27]. Within neurons MPP^+ is concentrated in mitochondria and inhibits complex I (NADH:ubiquinone oxidoreductase) of the electron transport chain [28,29]. As a consequence of impaired electron flux through complex I, mitochondrial ATP production is decreased while the generation of reactive oxygen and nitrogen species is increased [30–36]. The downstream events leading ultimately to neuronal cell death seem to be complex and involve activation of pro-apoptotic Bcl-2 family members, p53, JNK, and caspases as well as inflammation [18,37–43].

Insights into the molecular actions of MPTP brought up the question whether complex I activities might be impaired in patients suffering from sporadic PD. Indeed, complex I activities were reported to be significantly reduced (in the range of 30%) in post-mortem substantia nigra of PD patients [44–47], and platelets from PD patients [48–51], while data from skeletal muscle and other non-neuronal tissues are not consistent [52–56]. Although the complex I deficiency was first reported to be specific for the substantia nigra [57], a 30% reduction in complex I activity was recently detected also in frontal cortex mitochondria from PD postmortem brain [58,59]. Interestingly, Keeney et al. could demonstrate that catalytic subunits of complex I derived from PD frontal cortex mitochondria are oxidatively damaged, correlating with complex I misassembly and dysfunction [59]. Whether this increase in oxidative damage is specific for complex I and which subunits are affected has not been addressed so far.

In conclusion, several lines of evidence substantiated a link between PD and complex I activity. Discrepant reports on complex I activities in PD patients may best be explained by methodological issues, in particular sample preparation and assay technique. It is also conceivable that variations in the extent of complex I deficiency or differences between brain and peripheral tissues reflect the fact that PD is not a uniform entity, but rather an etiologically and pathologically heterogeneous syndrome.

1.1.1.2. Complex I and oxidative stress. Transport of electrons through complexes I–IV in the inner mitochondrial membrane involves a series of coupled redox reactions, which provide the energy to create a proton gradient across the inner mitochondrial membrane. Reducing equivalents from catabolic processes enter the electron transport chain (ETC) as NADH (at complex I) or $FADH_2$ (at complex II). Electrons from NADH or $FADH_2$ are passed on in a stepwise fashion until they reduce oxygen to water at complex IV. The movement of protons from the mitochondrial matrix to the intermembrane space creates an electrochemical gradient across the inner mitochondrial membrane. The electrochemical gradient, also called proton-motive force, is composed of a pH gradient (ΔpH) and an electrical potential ($\Delta\psi$) and drives ATP synthesis from ADP as protons re-enter the matrix through the ATP synthase (complex V). The whole process is called oxidative phosphorylation.

Complex I is the main gateway for electrons to enter the respiratory chain (rev. in refs. [60,61]). It consists of 14 central and up to 32 accessory subunits, which form an L-shaped complex with a membrane arm and a peripheral arm protruding into the mitochondrial matrix. Seven hydrophobic subunits forming the membrane central core are encoded by mitochondrial (mt) DNA. Complex I catalyzes the electron transfer from NADH (derived from the tricarboxylic acid cycle) to ubiquinone involving a flavine mononucleotide (FMN) and seven iron–sulfur clusters. This activity is coupled to the pumping of four protons across the inner mitochondrial membrane and thus to the formation of an electrochemical membrane potential. Remarkably, the reaction catalyzed by complex I is fully reversible, a fact that helps to explain reverse electron transport (see below) [62,63].

A plethora of studies established that mitochondria are an important source of reactive oxygen species (ROS) (rev. in refs. [64–66]). Increased formation of mitochondrial ROS and/or defective ROS removal by mitochondrial defence systems results in oxidative damage to mtDNA, proteins and lipids and perturbs redox signaling pathways [67]. Oxidative damage to mtDNA may compromise respiratory chain subunits encoded by mtDNA, thereby establishing a vicious circle of oxidative stress and bioenergetic failure, which has been the rationale for the mitochondrial theory of aging [68,69]. The extent, sources and mechanisms of mitochondrial ROS production as well as its physiological and pathophysiological relevance is still a matter of intense discussion (rev. in refs. [70–73]). There is increasing evidence that ROS are not just the bad guys, but have physiological functions as signaling molecules in diverse cellular pathways (rev. in refs. [74–76]). Moreover, a mild increase in ROS formation may activate protective stress response pathways [77,78]. Hence, the common paradigm that mitochondrial dysfunction is intimately linked to increased oxidative stress which promotes aging and neurodegenerative diseases is not unequivocally accepted. Several aspects have to be taken into consideration which might help to explain some controversial findings: First, mechanistic and quantitative studies on mitochondrial function in vivo are technically demanding, as many of the parameters are highly dynamic. Therefore most studies on mitochondrial ROS production have been performed with isolated mitochondria, submitochondrial particles or purified ETC complexes. It is now widely accepted that experimental conditions, such as the nature of substrates, oxygen concentration in the medium and respiration status strongly influence the results. Second, results from studies using isolated ex vivo mitochondria cannot easily be transferred to the in vivo situation, as the metabolic state of mitochondria seems to be highly variable and dynamic and in addition is influenced by spatial and temporal differences in the intracellular environment. These considerations are particularly important for neuronal mitochondria, which can be located at subcellular sites with different energy requirements and rapid changes in signaling molecules, such as axons and dendrites. Third, genetic mouse models might display unexpected or misleading phenotypes due to a strong compensatory capacity.

Complex I and to a lower extent complex III of the ETC are considered to be the main sites of ROS production which results from the transfer of a single electron to oxygen to generate the superoxide anion. The superoxide anion is the proximal mitochondrial ROS mainly produced in the mitochondrial matrix, where it is rapidly converted to hydrogen peroxide catalyzed by MnSOD. In the presence of metal ions such as Fe^{2+}, hydrogen peroxide can be converted to the highly reactive hydroxyl radical (Fenton reaction). The amount of

mitochondrial superoxide anion production is variable and influenced by a plenitude of factors: the nature of substrates, the potential at the inner mitochondrial membrane, the pH in the matrix and the local oxygen concentration (rev. in refs. [64,66,67]). The following conditions favor ROS production at complex I: (1) a low ATP production leading to a high proton-motive force and a reduced ubiquinone pool; and (2) a high NADH/NAD^+ ratio in the matrix, for example when the respiratory chain is damaged or the ATP demand is low. In mitochondria that actively produce ATP and therefore have a lower proton-motive force (ΔpH and $\Delta\psi$) and NADH/NAD^+ ratio, ROS production is low. ROS formation at complex I is significantly increased during reverse electron transport which occurs when electron supply from succinate (increased during exercise and in hypoxic tissue), glycerol-3-phosphate or fatty acid oxidation reduces the ubiquinone pool and forces electrons from ubiquinol uphill to complex I under conditions of a high proton-motive force. Under these conditions NAD^+ is reduced to NADH and ubiquinol is oxidized to ubiquinone at complex I.

The cause and the consequences of complex I deficiency in PD are not well understood. It has been suggested that mutations in complex I genes in the mitochondrial or nuclear genome can account for a dysfunction in complex I activity, assembly and/or stability. Many studies on complex I inhibition and ROS formation have been performed with rotenone, an inhibitor of complex I that binds in proximity to the quinone-binding site. When pyruvate or glutamate plus malate are used as substrates to generate NADH and induce forward electron transport, rotenone blocks proton pumping and increases superoxide generation [79]. During reverse electron transport, for example when succinate is used as a substrate, rotenone can block superoxide formation. In addition to the substrates present, the components of the proton-motive force (ΔpH and $\Delta\psi$) across the mitochondrial inner membrane have a strong impact on superoxide production with a more alkaline pH or a high membrane potential favoring ROS production [65,79].

Increased oxidative damage has been observed in several cellular and animal models of drug-induced complex I inhibition [30–35,80] (for reviews, see refs. [73,81–83]). In this context it is interesting to note that the first genetic mouse model for complex I deficiency has recently been published [84]. Mice lacking the NDUFS4 gene (NADH: ubiquinone oxidoreductase iron–sulfur protein 4) developed progressive encephalomyopathy at 5 weeks of age leading to death at 7 weeks. The abundance of intact complex I and complex I-driven oxygen consumption were significantly reduced, indicating that NDUFS4 may help to assemble and/or stabilize complex I. Remarkably, ATP levels were in the normal range and total oxygen consumption was unaffected in NDUFS4 knockout mice. Moreover, the authors of this study reported that they did not observe increased ROS formation in neuronal cultures derived from these mice. To add another layer of complexity, primary mesencephalic cultures from NDUFS4 knockout mice did not show an increased rate of cell death. Moreover, they were not protected from cell death induced by MPP^+ and rotenone [85]. These findings are surprising as they do not support the link between complex I deficiency, ATP depletion, oxidative stress and dopaminergic neuron death, which has been put forward to explain pathophysiological events leading to PD. A plausible explanation would be that these mice do not reflect the gradual decline in complex I activity which may persist over decades during the pathogenesis of PD in an aging individual. However, it might well be that complex I inhibition is not primarily responsible for the toxicitiy of MPP^+ and rotenone in dopaminergic neurons. Clearly, more in vivo models are needed to address the role of complex I deficiency in PD.

2. Mitochondrial DNA mutations

MtDNA is a double-stranded circular genome of about 16.6 kb, which replicates independently from the cell cycle and nuclear DNA replication. It encodes 13 proteins, all of which are subunits of respiratory chain complexes: seven subunits of complex I, one subunit of complex III, three subunits of complex IV and two of ATP synthase. In addition, mtDNA codes for 22 tRNAs and two rRNAs that are necessary for mitochondrial protein synthesis (rev. in refs. [86]). Mitochondria contain about 1500 different proteins, thus the majority of mitochondrial proteins is encoded by nuclear DNA, translated in the cytoplasm and imported into mitochondria by an elaborate import machinery (for review see refs. [87–89]). The multiple copies of mitochondrial DNA (1000–10,000 per mitochondrion) are arranged in nucleoids, which consist of several mtDNA molecules together with proteins necessary for mitochondrial replication and transcription, such as the mitochondrial transcription factor A (TFAM). MtDNA is characterized by an increased vulnerability to mutations, based on less efficient DNA repair mechanisms and the absence of protective histones. In addition, the proximity of the respiratory chain has been suggested to favor mtDNA damage by ROS. MtDNA mutations are inherited maternally or acquired. The high copy number confers some protective genetic redundancy, and usually, point mutations or large-scale deletions of the mtDNA co-exist together with wildtype mtDNA within a single mitochondrion, a condition which is known as heteroplasmy (rev. in refs. [70,86,90]). By a process called clonal expansion the mtDNA mutations can spread to daughter mitochondria and daughter cells (in mitotic tissue), leading to respiratory deficiency when a certain threshold of mutant mtDNA is exceeded [91]. Typically, mutations in the mitochondrial genome cause symptoms in postmitotic cells with high energy demands, in particular neurons and skeletal and cardiac muscle cells, resulting in encephalomyopathies (rev. in refs. [86,90,92]). However, accumulation of somatic mtDNA mutations occur also during aging in various tissues, such as brain and muscle (rev. in refs. [70,71]).

An age-dependent increase in somatic mtDNA deletions associated with a respiratory chain defect has been identified in dopaminergic neurons from the substantia nigra by using long-range PCR and quantitative real time or single molecule PCR [93,94]. Different neurons from the same individual showed unique mtDNA deletions, implying that they originated from clonal expansion. High levels (>60%) of mtDNA deletions were found in neurons deficient for cytochrome *c* oxidase (COX, complex IV), three catalytic subunits of which are encoded by mt DNA. These observations suggest that the increase in mtDNA deletions above a critical threshold might be causally related to respiratory chain deficiency. Bender et al. reported that levels of mtDNA deletions were slightly higher in dopaminergic neurons from PD patients in comparison to age-matched controls. Accumulation of mtDNA deletions was not observed in hippocampal neurons, pyramidal neurons of the cerbral cortex or cerebellar Purkinje cells of aged individuals, indicating a highly specific process. Interestingly, there seems to be no differences in the nature of aging- or disease-related mtDNA deletions detected in single substantia nigra neurons [95]. It will now be important to address the question why dopaminergic neurons of the substantia nigra are particularly vulnerable to mtDNA deletions. Both, the high oxidative burden within these cells and defective mtDNA replication could contribute to this selective vulnerability. In this context it may be interesting to note that patients with mutations in the gene encoding mitochondrial DNA polymerase (POLG) accumulate multiple mtDNA mutations and develop parkinsonism [96]. In addition, variants in the POLG CAG-repeat region, encoding a polyglutamine tract, seem to be a predisposing factor in sporadic PD [97].

A link between mtDNA and neurodegeneration has further been substantiated by genetic mouse models. A conditional knockout of TFAM in midbrain dopaminergic neurons caused reduced mtDNA expression, respiratory chain deficiency and neuronal cell death, leading to progressive, L-dopa-responsive impairment of motor functions [98].

There are several reports linking PD to specific mtDNA haplogroups or mtDNA point mutations, but not all of them could be confirmed in other studies (rev. in refs. [6,86]). Clearly, maternally inherited mtDNA mutations seem to be rarely associated with PD. By using the cybrid technique it has been observed that mtDNA from PD patients induces a complex I defect in healthy recipient cells, leading to the conclusion that complex I deficiency at least in some PD patients might be a systemic phenomenon [99–101]. To generate cybrid (which stands for cytoplasmic hybrid) cells, cultured human cells are depleted of mtDNA by long-term exposure to ethidium bromide. The resulting cells are then fused with platelets from PD patients or controls to re-introduce mtDNA. This approach has been challenged by another group using cybrid cells, reporting that alterations in respiratory chain activity do not correlate with PD mtDNA [102].

So far, there is no clear evidence that mtDNA mutations are the primary culprit for PD. MtDNA mutations rather occur in the context of increasing cellular stress and decreasing fidelity of cellular stress defence systems. Notwithstanding, clonal expansion of these mutations can functionally impair the respiratory capacity and thus precipitate degeneration of vulnerable neuronal populations.

2.1. Familial PD and mitochondria

Since 1997 when α-synuclein was described as the first gene associated with familial PD, four other genes have conclusively been linked to autosomal recessive (parkin, PINK1, DJ-1) or dominant (LRRK2) parkinsonism (Table 1; for reviews on PD genetics see refs. [3,103–106]). Mutations in ATP13A2, encoding a P-type lysosomal ATPase, were identified in two kindreds with Kufor-Rakeb syndrome, a multisystemic neurodegenerative disorder which in addition to juvenile/early-onset parkinsonism shows pyramidal tract dysfunction and cognitive impairment [107]. However, ATP13A2 mutations have also been found in rare cases with juvenile parkinsonism and only mild additional, atypical features [108].

Familial variants of PD account for up to 10% of PD cases. They usually, but not exclusively, show an early onset of symptoms and are in essence clinically indistinguishable from sporadic PD [103,106]. Remarkably, what we know so far about the function and dysfunction of PD genes confirms the relevance of the biochemical alterations found in sporadic PD, i.e., mitochondrial dysfunction, oxidative stress and a dysbalance in protein homeostasis characterized by an increase in protein misfolding and aggregation accompanied by an impaired removal of misfolded proteins. Indeed, several PD genes have been associated with mitochondrial integrity and cellular stress response and quality control systems (rev. in refs. [109–114]). Thus, insight into the function of PD genes can promote our understanding of the molecular causes of PD and help to focus research on key biochemical pathways.

2.1.1. PINK1

2.1.1.1. PINK1 and mitochondrial function. Mutations in the PINK1 (PTEN-induced putative kinase) gene are the second most common cause of autosomal recessive, early-onset parkinsonism after parkin mutations [115]. PINK1 is a 581 amino acid protein with an N-terminal mitochondrial targeting sequence and a serine/threonine kinase domain (rev. in refs. [116]). Most pathogenic mutations are missense mutations which cluster to the kinase domain and have been shown to impair the kinase activity, which is essential for the neuroprotective activity of PINK1. Increased PINK1 expression confers protection from apoptotic cell death in various stress paradigms, and loss of PINK1 function increases the vulnerability of cells to stress-induced cell death [115,117–120]. The effects of PINK1 deficiency on mitochondrial function and morphology are multifaceted, comprising decreases in mitochondrial membrane potential, complexes I and IV activities, ATP production, mitochondrial import and mtDNA levels, increases in ROS production and abnormal ultrastructural mitochondrial morphology [120–135]. The cause of all the effects observed and their timely order is still a matter of intense discussion. Morais et al. recently reported that disruption of complex I activity is an early event upon PINK1 loss of function, responsible for mitochondrial membrane depolarization, increased sensitivity to apoptotic stress and synaptic transmission deficits, exemplified by an impaired mobilization of reserve pool vesicles after rapid stimulation in *Drosophila* neuromuscular junctions [132]. Ghandi et al. demonstrated that impaired respiration in PINK1-deficient neurons can be restored by providing substrates of complexes I and II, implying that respiratory complexes are intact [121]. They observed that PINK1 deficiency causes a dysbalance of calcium homeostasis with a higher basal mitochondrial calcium concentration and mitochondrial calcium overload under stress conditions, which was traced back to a dysfunction of the Na^+/Ca^{2+} exchanger at the inner mitochondrial membrane. The Na^+/Ca^{2+} exchanger mediates extrusion of calcium from mitochondria, but so far has not been characterized on a molecular level. Thus, the mechanism of the functional interaction between PINK1 and this exchanger could not be analyzed. However, the data suggest that the impairment of mitochondrial calcium efflux promotes ROS production that inhibits glucose uptake, resulting in reduced substrate delivery and respiration. The dysbalance in calcium homeostasis was placed at the top of these events, as substrate supply could overcome impaired respiration and reduction of ROS production restored glucose uptake, but neither substrate provision nor ROS reduction was able to affect mitochondrial calcium overload in PINK1-deficient cells [121]. Alterations in calcium homeostasis were also observed in cultured cells co-expressing a pathogenic PINK1 mutant (W437X) and A53T α-synuclein [128]. In this model, mutant PINK1 aggravated mitochondrial damage induced by α-synuclein, such as mitochondrial membrane depolarization and increased mitochondrial size with loss of cristae, and in addition decreased cellular ATP production. Interestingly, a blocker of mitochondrial calcium influx completely restored mitochondrial membrane potential and ATP production in cells expressing mutant α-synuclein and mutant PINK1.

Weihofen et al. recently linked PINK1 to mitochondrial trafficking [131]. Immunopurification of PINK1 from a mitochondria-enriched fraction of HEK293-FT cells expressing FLAG-tagged PINK1 and subsequent mass spectrometry of PINK1 complexes revealed that PINK1 interacts with the atypical GTPase miro, implicated in mitochondrial trafficking, and the inner mitochondrial membrane protein mitofilin, which has been described to control cristae morphology [136]. Miro is an outer mitochondrial membrane protein which interacts with the adaptor protein milton to link kinesin-1 heavy chains to mitochondria for their anterograde axonal transport (rev. in refs. [137,138]). Overexpression of either miro or milton recruited PINK1 to mitochondria. Even the mitochondrial localization of mutant PINK1 lacking the N-terminal mitochondrial targeting sequence (Δ1–111) was markedly increased by miro or milton. Moreover, increased expression of miro or milton could rescue alterations in mitochondrial morphology in PINK1-deficient cells. It will now be interesting to address the question whether mitochondrial transport is impaired in PINK1-deficient neurons and whether

Table 1
PD-associated loci and genes with conclusive evidence.

PD locus	Chromosomal localization	Gene product	Mode of inheritance
PARK1/4	4q21-q23	α-synuclein	autosomal dominant
PARK2	6q25-q27	parkin	autosomal recessive
PARK6	1p36-p35	PINK1	autosomal recessive
PARK7	1p36	DJ-1	autosomal recessive
PARK8	12p11-q13	LRRK2	autosomal dominant
PARK9	1p36	ATP13A2	autosomal recessive

expression of miro and milton is essential for the neuroprotective activity of PINK1.

2.1.1.2. PINK1 substrates. Two putative PINK1 substrates have been identified to date by affinity purification approaches. Pridgeon et al. found that PINK1 phosphorylates mitochondrial TRAP1 (TNFR-associated protein 1; heat shock protein 75) and that the protective activity of PINK1 against oxidative stress is dependent on TRAP1 phosphorylation [139]. Plun-Favreau et al. provided evidence for a functional link beween PINK1 and HtrA2/Omi, a mitochondrial serine protease which is released to the cytosol by apoptotic stimuli and interacts with IAPs (inhibitor of apoptosis proteins). They showed that PINK1 expression is important for phosphorylation of HtrA2/Omi on serine 142, which is most likely mediated by the p38 stress kinase pathway, but depends on a direct interaction of HtrA2/Omi with PINK1 [140]. Thus, PINK1 might serve as an adaptor between HtrA2/Omi and the p38 kinase. Phosphomimetic HtrA2/Omi mutants were characterized by an increase in protease activity accompanied by an enhanced ability to protect cells from rotenone- or 6-OHDA-induced stress. This led the authors to conclude that PINK1 and HtrA2/Omi act in the same pathway. The effects downstream of phosphorylated HtrA2/Omi are not well understood, but it seems plausible that HtrA2/Omi is involved in the quality control of intermembrane space proteins, either by degrading misfolded and damaged proteins or by transducing a stress response signal, similarly to its bacterial homologs DegP and DegS [141]. HtrA2/Omi is an attractive candidate for PD, since HtrA2/Omi loss-of-function mice show neurodegeneration with parkinsonian features, indicating that HtrA2/Omi can serve a neuroprotective function [142,143]. Mutations in the gene encoding HtrA2/Omi have been reported in PD patients [144,145], however, linkage evidence is lacking to proof pathogenicity [146,147].

2.1.1.3. Subcellular localization of PINK1. PINK1 has been reported to reside in the mitochondrial intermembrane space, the inner and outer mitochondrial membrane and in the cytosol, and so far it is not clear how the different findings can be explained [119,139,140,148–156]. It is conceivable that the destination of PINK1 is dependent on specific cellular conditions, a phenomenon which could contribute to the regulation of PINK1 activity. A limitation in the analysis of PINK1 trafficking is the lack of antibodies which efficiently detect endogenous PINK1 in neurons. Consequently, most studies are performed with overexpressed PINK1, which may create artifacts by overloading the mitochondrial import machinery. It has been demonstrated that the N-terminal 34 or 77 amino acids of PINK1 are sufficient to confer mitochondrial targeting [151,153]. In addition to full-length PINK1 (66 kDa) at least two proteolytically processed variants of 55 and 46 kDa can be found, suggesting cleavage of PINK1 by mitochondrial processing peptidases. In conclusion, there are still many open questions regarding (1) the precise subcellular localization and origin of different PINK1 species, i.d. whether smaller PINK1 species occuring in the cytosol have been N-terminally processed by mitochondrial peptidases or result from cytosolic proteolysis, (2) conditions that might influence its targeting and (3) whether the localization in different compartments affects the biochemical features and functional activity of PINK1. Intriguingly, a PINK1 mutant lacking the N-terminal mitochondrial targeting sequence (Δ1–111) has recently been shown to provide protection against MTPT-induced toxicity similarly to wildtype PINK1 both in cultured primary cortical neurons and mice [119].

2.1.2. Parkin

2.1.2.1. Parkin and ubiquitylation pathways. In 1998, mutations in the parkin gene were identified as a cause of autosomal recessive PD with juvenile onset in Japanese families [157]. Since then, more than hundred different mutations have been described in patients of diverse ethnic backgrounds, accounting for the majority of autosomal recessive parkinsonism [158,159]. The parkin gene encodes a cytosolic 465 amino acid protein with a ubiquitin-like domain (UBL) at the N-terminus and a RBR domain close to the C-terminus, consisting of two RING finger motifs which flank a cysteine-rich in-between RING finger domain. The presence of the RBR domain suggested that parkin has an E3 ubiquitin ligase activity, mediating the covalent attachment of ubiquitin to substrate proteins. A well known function of ubiquitin is to target substrates for degradation by the proteasome, which requires a chain of at least four ubiquitin moieties in length. Genetic and biochemical studies revealed that pathogenic mutations induce a loss of parkin function, leading to the hypothesis that the accumulation of parkin substrates causes neurotoxicity and results in the death of dopaminergic neurons. From yeast-two-hybrid and pull-down approaches a long list of putative parkin substrates has emerged (rev. in ref. [160]). Curiously, these substrates do not fit into a common pathway and so far did not contribute mechanistic insight into the functional role of parkin. Moreover, data on the accumulation of putative parkin substrates in parkin knockout mice or brains from patients carrying parkin mutations are conflicting. There is increasing experimental evidence that parkin can induce proteasome-independent ubiquitylation [161–166]. Depending on the number of ubiquitin moieties attached and the mode of ubiquitin linkage, ubiquitylation serves a remarkably wide range of physiological functions (rev. in refs. [167–170]). Ubiquitin harbors seven lysine residues, which in principle can all engage in the formation of polyubiquitin chains. Ubiquitin linkage via lysine 48 most commonly targets proteins for proteasomal degradation, while linkage via lysine 63 has several regulatory roles, implicated in signal transduction, DNA repair, membrane protein trafficking, endocytosis and autophagy. In addition, monoubiquitylation and multiple monoubiquitylation of a substrate protein can occur, which also control various physiological processes. Under experimental conditions, parkin can apparently catalyze different modes of ubiquitylation, however, it is currently not clear, whether the multifaceted activity of parkin under in vitro conditions is of relevance in the physiological context.

2.1.2.2. Parkin: an all-purpose neuroprotective protein. The most impressive and reproducible activity of parkin is its wide neuroprotective capacity. Parkin can protect cells against a remarkably wide spectrum of stressors, including mitochondrial dysfunction, excitotoxicity, endoplasmic reticulum stress, proteasome inhibition and overexpression of α-synuclein, tau, Aβ peptide or expanded polyglutamine fragments (rev. in refs. [160,171]). In line with a central role of parkin in maintaining neuronal viability, parkin gene expression is up-regulated in various stress paradigms [164,172–175]. Recent research revealed that the neuroprotective activity of parkin is associated with proteasome-independent ubiquitylation [162,164]. However, this finding does not exclude the possibility that parkin can target some substrates for proteasomal degradation.

Notably, parkin could play a more general role in the pathogenesis of sporadic PD based on the fact that parkin is prone to misfolding (rev. in refs. [171,176]). We and others could show that several pathogenic mutations as well as severe oxidative stress induce the formation of non-native, non-functional parkin [163,177–187]. Remarkably, LaVoie et al. could demonstrate that misfolded parkin occurs in the substantia nigra of sporadic PD patients [188]. In support of this concept, parkin can be inactivated by nitrosative stress and *S*-nitrosylated parkin has also been detected in the brains of sporadic PD patients [189,190].

2.1.2.3. Parkin and mitochondria. One of the first links between parkin and mitochondria was provided by Darios et al. who observed that parkin prevents mitochondrial swelling and cytochrome *c* release in ceramide-treated cells [191]. Another important finding of this

study was that a small fraction of parkin can physically interact with the outer mitochondrial membrane, both in parkin-overexpressing cells and mouse brain. Prevention of cytochrome *c* release by parkin was recently confirmed by using a cell-free in vitro assay. Berger et al. presented evidence that the expression levels of parkin are inversely correlated with cytochrome *c* release induced by BH3 domains of pro-apoptotic proteins [192]. Interestingly, PINK1, which seems to be functionally linked with parkin (see Section 2.2.4), had no effect on cytochrome *c* release. Moreover, the association of parkin with mitochondria is apparently not sufficient for the inhibition of evoked cytochrome *c* release; parkin had to be expressed in life cells prior to isolation of mitochondria to prevent cytochrome *c* release [192]. Localization of parkin at the outer mitochondrial membrane has also been observed by Stichel et al. who performed an ultrastructural analysis of adult mouse brain [193]. Kuroda et al. found parkin exclusively inside mitochondria in proliferating SH-SY5Y cells, where it binds to the mitochondrial transcription factor TFAM to stimulate mitochondrial replication and transcription [194]. When cells were placed under differentiated or quiescent (treatment with anti-proliferative agents) conditions, parkin moved to the cytoplasm via the permeability transition pore. By using a chromatin immunoprecipitation approach, binding of endogenous parkin to mtDNA in proliferating, but also differentiated SH-SY5Y cells and even mouse brain tissue was recently demonstrated by Rothfuss et al. [195]. The authors of this study confirmed that ectopic expression of parkin enhances replication of the mitochondrial genome and transcription of mitochondrial genes. In addition, parkin was found to protect mtDNA from oxidative damage and to stimulate mtDNA repair [195]. It will now be important to address the questions of how parkin can enter mitochondria, which conditions enhance its mitochondrial localization and which target(s) parkin may have inside mitochondria. Whatever the precise mechanism might be, the capacity of parkin to protect cells against mitochondrial toxins was demonstrated in various cellular and animal models [164,191,196–201].

A proteomic approach using ventral midbrain of parkin knockout mice revealed a decreased abundance of some proteins involved in mitochondrial function (subunits of complexes I and IV) and the oxidative stress response [202]. Of note, the authors of this study presented evidence for a reduced respiratory capacity of striatal mitochondria isolated from parkin knockout mice, while the gross mitochondrial morphology appeared normal. Another proteome study indicated that a high proportion of differentially expressed proteins in cortical or striatal tissue derived from parkin knockout mice was related to energy metabolism, probably reflecting an adaptive regulation of bioenergetics in response to parkin loss of function [203]. Stichel et al. performed a comprehensive ultrastructural analysis of mitochondrial morphology in parkin knockout mice, A30P/A53T α-synuclein transgenic mice, and double mutant mice (parkin knockout × A30P/A53T α-synuclein transgenic mice) and reported age- and tissue-specific changes in both mono- and double-mutant mice [204]. None of these transgenic mice developed overt motor disabilities or gross histopathological abnormalities. However, marked alterations in mitochondrial architecture, such as dilated and disorganized cristae, were observed in the substantia nigra and cortex, but not in the skeletal muscle cells of aged (12–14 months) double-mutant mice. Even though cortical mitochondria were significantly damaged, the respiration capacity of complex I was only compromised in the substantia nigra, suggesting that dopaminergic neurons are particularly vulnerable to mitochondrial damage.

Several studies analyzed mitochondrial features in tissues from parkin-mutant patients. Müftüoglu et al. measured complexes I and IV activities in mitochondria isolated from leukocytes [205]. A significant decrease (by about 60%) in complex I activity was found both in patients with parkin mutations and sporadic PD patients, whereas complex IV activity was only reduced in sporadic PD patients. Cultured fibroblasts from parkin mutant patients showed morphological and functional mitochondrial defects, i.e. a decrease in the membrane potential (by 30%), complex I activity (by 45%), ATP production (by 58%) and an increase in rotenone-induced mitochondrial fragmentation [206]. In the study of Rothfuss et al. parkin mutant fibroblasts were characterized by a 22% reduction in the mtDNA copy number and an increased vulnerability to oxidative stress-induced mtDNA damage [195].

2.1.2.4. A functional link between parkin and PINK1. Similarly to parkin knockout mice, PINK1-deficient mice do not display degeneration of dopaminergic neurons, but only some mild alterations in dopaminergic neurotransmission. In PINK1 knockout mice (Δexons 4–7) a decrease in evoked striatal dopamine release and subsequent impairment of synaptic plasticity has been observed [207]. Curiously, an increase of extracellular striatal dopamine occurred in some parkin knockout mice (Δexon3; [208,209]. Gautier et al. reported a subtle increase in larger, but ultrastructurally normal mitochondria, a mild reduction in mitochondrial respiration in the striatum of young (3–4 months) and in the cortex of aged (22–24 months) PINK1 knockout mice, which, however, did not lead to reduced ATP levels [122]. Even in aged PINK1 knockout mice levels of oxidative stress markers were unchanged. In a different PINK1 knockout mouse line Gispert et al. observed progressive reduction of body weight and spontaneous locomotor activity in the absence of nigrostriatal degeneration [124]. Whether locomotor deficits in these mice were L-dopa responsive has not been reported. Furthermore, import of pre-proteins in liver mitochondria from these PINK1-deficient mice was impaired in an age-dependent manner [124]. This is an interesting observation which raises the question whether PINK1 per se has an effect on mitochondrial import or whether the defective import observed in PINK1-deficient mice is a consequence of the reduced mitochondrial membrane potential.

In contrast to parkin and PINK1 knockout mice, *Drosophila* null mutants show a striking and remarkably similar phenotype, characterized by reduced life span, male sterility, and locomotor defects due to apoptotic flight muscle degeneration [210–214]. The earliest manifestation of muscle degeneration and defective spermatogenesis was mitochondrial pathology, exemplified by swollen mitochondria and disintegrated cristae [210]. Strikingly, parkin could compensate for the PINK1 loss-of-function phenotype, but not vice versa, implying that PINK1 and parkin function in a common genetic pathway with parkin acting downstream of PINK1 [211–213]. Subsequent studies in *Drosophila* suggested that parkin and PINK1 may have a possible role in modulating mitochondrial morphology and dynamics [215–218] (see Fig. 1 for an overview of mitochondrial dynamics). In flies, the parkin or PINK1 flight muscle phenotype was suppressed by an increase in mitochondrial fission or a decrease in fusion, leading to the conclusion that the PINK1/parkin pathway promotes mitochondrial fission. In parallel, we performed studies in cultured human cells and confirmed that parkin can compensate for the alterations in mitochondrial morphology induced by siRNA-mediated down-regulation of PINK1 [134]. Notably, transient silencing of parkin in dopaminergic SH-SY5Y showed a mitochondrial phenotype remarkably similar to that of PINK1 deficiency, characterized by a marked increase in mitochondrial fragmentation and a decrease in overall ATP production [135]. Both the morphological and functional deficits could be prevented by the enhanced expression of the fusion-promoting proteins Mfn2 or OPA1. Likewise, a dominant negative mutant of the fission-promoting protein Drp1 was protective, suggesting that a decrease in mitochondrial fusion or an increase in fission is associated with a loss of parkin or PINK1 function. The following findings established that an increase in mitochondrial fragmentation is responsible for the alterations observed in parkin- or PINK1-deficient cells. First, the mitochondrial phenotype in parkin- or PINK1 deficient cells was not observed in Drp1-deficient cells. Second,

A

Gene product	Role in mitochondrial dynamics	Localization
Mfn1/2	outer membrane fusion (GTPase)	outer mitochondrial membrane with the N- and C-termini facing the cytosol (U-shaped transmembrane domain)
OPA1	inner membrane fusion (GTPase)	inner mitochondrial membrane facing the intermembrane space
Drp1	fission (GTPase)	cytosol, during fission recruited to punctae at the outer mitochondrial membrane
Fis1	fission	outer mitochondrial membrane (transmembrane protein)

B

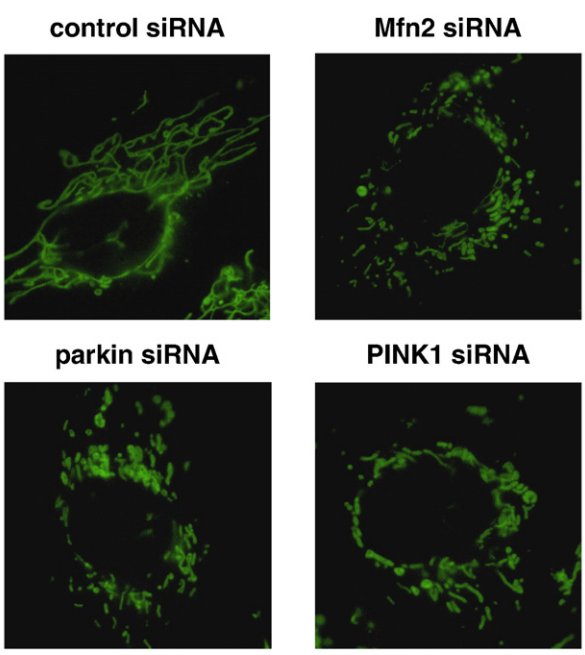

Fig. 1. Parkin, PINK1 and mitochondrial dynamics. (A) Key players of the mitochondrial fusion and fission machinery. For reviews on mitochondrial dynamics, see refs. [319-322]. (B) Transient down-regulation of parkin or PINK1 by RNA interference induces alterations in mitochondrial morphology in human SH-SY5Y cells. Control siRNA-transfected cells show a network of tubular mitochondria. Parkin or PINK1 loss of function results in mitochondrial fragmentation, which also occurs in Mfn2-deficient cells due to an relative increase in mitochondrial fission.

parkin as well as PINK1 suppressed mitochondrial fission induced by Drp1. At the same time Sandebring et al. reported very similar findings for a stable PINK1 knockdown in human dopaminergic M17 cells [130]. These authors used fluorescence recovery after photobleaching (FRAP) to show that PINK1 can reduce mitochondrial fragmentation induced by rotenone in a kinase-dependent fashion, whereas PINK1-deficient cells displayed a lower mitochondrial connectivity. In line with a study by Dagda et al. and our observations, knockdown of Drp1 prevented mitochondrial fragmentation caused by PINK1 loss of function [129,135]. Of note, mitochondrial fragmentation observed in parkin- or PINK1-deficient cells was not a consequence of increased apoptotic cell death [130,135]. The activity of Drp1 is regulated by posttranslational modifications, therefore Sandebring et al. analyzed whether in PINK1-deficient cells the phosphorylation status of Drp1 might be altered. They observed that a loss of PINK1 function is associated with a decrease in phospho-Drp1 levels and an increase in Drp1 GTPase activity. Calcineurin is a phosphatase known to dephosphorylate Drp1 at serine 637 [219], consequently, Sandebring et al. tested PINK1-deficient cells for expression levels and activity of calcineurin. They found that calcineurin activity was significantly increased in PINK1 knockdown cells, while expression levels were not affected. Interestingly, the calcineurin inhibitor FK506 could rescue mitochondrial fragmentation caused by a loss of PINK1 function. These findings add to the notion that calcium homeostasis is impaired in PINK1-deficient cells [121,128].

Obviously, the findings in mammalian parkin- or PINK1-deficient cells are strikingly different to those reported in the fly models. How can these discrepancies be explained? To address this question experimentally, we performed a comparative analysis of the

consequences of parkin or PINK1 down-regulation in human, mouse and insect cells [135]. Notably, mitochondrial fragmentation turned out to be an early response to parkin or PINK1 loss of function which also occurred in primary mouse neurons and *Drosophila* S2 cells. In addition, the mitochondrial phenotype was more pronounced after transient silencing in comparison to stable knockdown conditions, suggesting that compensatory mechanisms can rapidly be activated. This might explain why mitochondrial fragmentation in PINK1-deficient cells was observed in some, but not all studies and why parkin or PINK1 knockout mice do not display gross alterations in mitochondrial morphology. It is conceivable that compensatory strategies might not be sufficient to maintain mitochondrial integrity in parkin- or PINK1-deficient cells under stress conditions. Indeed, different studies reported mitochondrial fragmentation and functional deficits in cultured skin fibroblasts from parkin- or PINK1-mutant patients upon cellular stress [126,134,206].

What can we learn from the discrepant findings in *Drosophila* and mammalian models? First, it seems rather unlikely that parkin and PINK1 directly regulate mitochondrial dynamics. Regulation of mitochondrial dynamics might be more sophisticated in mammals [220], but in general, the fusion and fission machinery is highly conserved. Thus, it is implausible that parkin/PINK1 promote fission in flies and prevent fission in mammals. Second, the *Drosophila* models without any doubt have a lot of advantages, but we should keep in mind that for some aspects there seem to be differences between flies and humans. In particular, *Drosophila* flight muscles and eyes are highly specialized tissues. We observed that an increase in mitochondrial fragmentation occurs early upon parkin/PINK1 silencing both in cultured human and *Drosophila* cells [135]. Thus, the most plausible explanation for the discrepant findings is that the compensatory strategies in flies and mammals are different. The accumulation of damaged mitochondria in parkin/PINK1-deficient flies might be a stimulus to activate fusion in an attempt to dilute these dysfunctional mitochondria. However, in tissues with high energy demands, such as flight muscles or spermatids, this strategy might not be beneficial in the end, as increased fusion eventually leads to the contamination of the whole mitochondrial network with dysfunctional contents [221]. This might explain why parkin/PINK1 null flies show a phenotype in such tissues that can be rescued by increasing fission, possibly favoring the elimination of dysfunctional mitochondria by autophagy [222]. In support of this concept, a recent study proposed that parkin can promote mitophagy, i.e., the autophagic clearance of dysfunctional mitochondria [223]. Narendra et al. presented evidence that treatment of HEK293 cells with the uncoupler CCCP (carbonyl cyanide 3-chlorophenylhydrazone) induces recruitment of parkin to depolarized mitochondria within one hour. The authors then turned to HeLa cells, which do not express endogenous parkin due to the localization of the parkin gene within FRA6E (6q26), a common fragile site of the human genome that is frequently mutated in ovarian tumors [224]. After 48 h of CCCP treatment, no mitochondria were detectable by immunocytochemistry in HeLa cells overexpressing YFP-parkin, suggesting that parkin can induce the removal of damaged mitochondria. Clearance of depolarized mitochondria by parkin did not occur in autophagy-deficient ATG5 knockout mouse embryonic fibroblasts, which indicates that autophagosome formation is essential for this effect. The study by Narendra et al. provided fundamental new insight into the role of parkin in mitochondrial quality control and opens new avenues for further investigations. First, a role in regulating mitophagy has to be proven for endogenous parkin. Likewise, are pathogenic parkin mutants impaired in this activity? However, the most important question is whether ubiquitylation activity of parkin is required for inducing mitophagy. Strikingly, ubiquitylation has recently emerged as a selective targeting signal for the autophagic clearance of various types of cargo (rev. in ref. [225]). An appealing scenario would be that parkin ubiquitylates a specific substrate at the mitochondrial membrane in response to stress conditions associated with a decrease of the mitochondrial membrane potential. Where and when could PINK1 enter the stage? Loss of PINK1 function has recently been reported to promote autophagy and mitophagy in SH-SY5Y cells, which was accompanied by an increase in mitochondrial fission and ROS production [129]. Dominant-negative Drp1 did not reduce mitochondrial ROS production, but scavenging superoxide anions inhibited autophagy in PINK1-deficient cells, suggesting that ROS are necessary for both mitochondrial fragmentation and autophagy. Interestingly, siRNA-mediated down-regulation of ATG7 or ATG8/LC3B, two proteins essential for autophagy, did not affect mitochondrial ROS production, but reversed mitochondrial fragmentation in PINK1-deficient cells. This finding points to a possible reciprocal interaction of the machineries regulating mitochondrial dynamics and autophagy. Furthermore, Dagda et al. reported that parkin overexpression increased mitophagy in PINK1-deficient cells. Thus, parkin and PINK1 appear to have different net effects on mitophagy, whereas the consequences of PINK1/parkin loss of function on mitochondrial morphology and function are strikingly similar both in mammalian and *Drosophila* models.

Based on the observation that PINK1 is partially located in the cytosol, there is in principle a chance for a cytosolic rendezvous of parkin and PINK1, possibly at the outer mitochondrial membrane. Indeed, a direct interaction of parkin and PINK1 has been observed. Kim et al. reported that PINK1 controls the mitochondrial localization of parkin by directly phosphorylating parkin at threonine 175 [226]. Um et al. observed that parkin binds to PINK1 and up-regulates expression of PINK1, which in turn reduces the solubility of parkin [227]. Shiba et al. show that parkin directly interacts with PINK1, leading to a stabilization of PINK1 by interference with its ubiquitylation and proteasomal degradation [228]. These are interesting observations, however they are based on the overexpression of parkin and PINK1. Studies in both *Drosophila* and mammalian cells are consistent in the finding that parkin can rescue PINK1 deficiency [134,135,211–213], thus parkin seems to act downstream of PINK1. However, for a functional interaction parkin and PINK1 not necessarily have to interact physically. It is also conceivable that PINK1 phosphorylates a mitochondrial protein upon stress which can activate a pathway converging at parkin or at a target downstream parkin. Obviously, PINK1 is not essential for parkin function, and consequently, the functional interaction of PINK1 and parkin might not fit into a simple, linear pathway. In line with a more complex link between parkin and PINK1, parkin can prevent evoked mitochondrial cytochrome *c* release, while PINK1 cannot [192]. Clearly, more studies are needed to unravel the role of parkin and PINK1 in mitochondrial protection, remodeling and clearance and the mechanism underlying their functional interaction.

Three recent studies in *Drosophila* addressed the role of HtrA2/Omi as another possible player in the PINK1/parkin game. While the fly studies are in agreement on the functional interaction of PINK1 and parkin, this is strikingly different for the role of HtrA2/Omi. Using ectopic expression in the *Drosophila* eye, Whithworth et al. observed that HtrA2/Omi genetically acts downstream of PINK1, but functions independently of parkin. They also showed that rhomboid-7 (presenilin-associated rhomboid-like [PARL] in mammals) is required to cleave the precursor forms of both PINK1 and HtrA2/Omi [229]. However, Yun et al. reported that HtrA2/Omi null mutants do not show defects in mitochondrial integrity [230]. In addition, they found no evidence for a genetic interaction between PINK1 and HtrA2/Omi in loss-of-function studies. Conversely, Tain et al. found mild mitochondrial defects in HtrA2/Omi null flies and observed that HtrA2/Omi can partially substitute for PINK1 loss of function [231]. PINK1/HtrA2/Omi double mutant flies showed a phenotype identical to that of PINK1 mutants, while the phenotype of parkin/HtrA2/Omi double mutants was stronger than that of either mutant alone, which

led the authors to conclude that parkin and HtrA2/Omi are both downstream effectors of PINK1, but act in parallel pathways.

2.1.3. DJ-1

Mutations in the DJ-1 gene, encoding a 189-amino acid protein, have been associated with rare cases of early onset autosomal recessive PD [232]. A large deletion and a missense mutation (L166P) leading to the rapid degradation of the mutant protein were the first mutations identified in patients, indicating that a loss of DJ-1 function can cause parkinsonism (rev. in refs. [233]). DJ-1 belongs to the ThiJ/PfpI family and shares structural similarities with the stress-inducible *Escherichia coli* chaperone Hsp31 [234].

Various functions have been ascribed to DJ-1. Clearly, overexpression of DJ-1 protects neurons from oxidative stress-induced damage and DJ-1 deficiency renders cells more susceptible to oxidative injury [197,235–242]. DJ-1 is converted into a more acidic pI variant in response to oxidative stress, due to the formation of cysteine–sulfinic acid at cysteine 106 [243–245]. Notably, cysteine 106 is essential for the neuroprotective activity of DJ-1 [237,244,246,247]. Studies on the subcellular localization of DJ-1 reported the presence of DJ-1 in cytosolic, mitochondrial and nuclear compartments; mitochondrial localization of DJ-1 was enhanced by oxidative stress [248–250]. Substitution of cysteine 106 by alanine interfered with both mitochondrial localization and protection against mitochondrial toxins [244]. Within mitochondria endogenous DJ-1 was found in the matrix and intermembrane space [251]. Junn et al. recently observed that endogenous DJ-1 translocates to mitochondria (within 3 h) and the nucleus (within 12 h) of human neuroblastoma cells in response to oxidative stress [252]. Interestingly, mitochondrial targeting of DJ-1 via fusion to a mitochondrial targeting signal sequence increased its neuroprotective activity. The authors of this study reported that the mutation of cysteines at positions 106, 53 or 46 had no impact on the mitochondrial localization of DJ-1 upon oxidative stress.

What might be the function of mitochondrial DJ-1? Isolated mitochondria from DJ-1 knockout mice showed a twofold increase in hydrogen peroxide accompanied by a reduction in mitochondrial aconitase activity, indicating a deficit in scavenging mitochondrial ROS [253]. By employing recombinant DJ-1 and mass spectrometry analysis, Andres-Mateos et al. demonstrated that DJ-1 is an atypical peroxiredoxin-like peroxidase and that cysteine 106 is the principal target for sulfinic acid formation.

Of note, DJ-1 could not compensate for the mitochondrial alterations observed in parkin- or PINK1-deficient cells, neither in the *Drosophila* model nor in cultured human cells, suggesting that it does not function within PINK1/parkin pathway [134,213].

2.1.4. α-Synuclein

Three missense mutations (A53T, A30P, E46K) as well as genomic duplication and triplication of the gene encoding α-synuclein have been identified in rare cases of familial PD [254–260]. α-Synuclein is the major component of Lewy bodies, therefore providing the most obvious link between sporadic and familial PD [1]. Despite enormous efforts, little is known about the physiological function of α-synuclein and its mechanism of toxicity. α-Synuclein is a 140-amino acid protein which is abundantly expressed in the central nervous system. Its enrichment in presynaptic terminals and its association with vesicles suggests a role in synaptic dynamics (rev. in refs. [261,262]). α-Synuclein is a natively unfolded or intrinsically disordered protein with considerable conformational plasticity (rev. in refs. [263–265]). Similarly to other misfolding-prone proteins, evidence accumulated that not the final α-synuclein aggregates, but rather oligomeric intermediates might be the toxic species (rev. in refs. [176,264,266,267]). Based on observations in different model systems various mechanisms have been proposed to explain the toxic effects of α-synuclein (rev. in refs. [267]), including impaired endoplasmic reticulum (ER) to Golgi vesicular trafficking and ER stress [268,269], impairment of proteasomal or lysosomal protein degradation [270–275], Golgi fragmentation [276], sequestration of anti-apoptotic proteins into aggregates [277], and the formation of pores on cellular membranes [278,279].

Several studies reported that a fraction of cytosolic α-synuclein can be found at or even within mitochondria in a regio-specific manner [280–283]. Binding of α-synuclein to mitochondria was enhanced by cytosolic acidification [284]. Perihar et al. observed cytochrome *c* release and an increase in mitochondrial calcium and nitric oxide in response to the association of α-synuclein with mitochondria [285]. Devi et al. showed that the N-terminal 32 amino acids of α-synuclein harbor a cryptic mitochondrial targeting signal directing α-synuclein to the inner mitochondrial membrane where it associates with complex I [286]. As a result, α-synuclein decreased complex I activity and increased ROS production in human fetal dopaminergic primary neuronal cultures overexpressing wildtype α-synuclein. Overexpression of A53T α-synuclein accelerated these effects. To substantiate their findings, Devi et al. determined the amount of mitochondrial α-synuclein in human brain and found a significant accumulation of α-synuclein in the substantia nigra and striatum from PD patients.

Further evidence for mitochondrial alterations was found in cellular and mouse models overexpressing wildtype or mutant α-synuclein, including ultrastructural abnormalities, reduced COX and complex IV activity, a decrease in the mitochondrial membrane potential, oxidation of mitochondria-associated metabolic proteins, and an increased sensitivity to mitochondrial toxins, possibly by increasing α-synuclein aggregation [204,287–294]. However, an increase in sensitivity to mitochondrial toxins in α-synuclein overexpressing mice was not observed in all studies [295,296]. α-Synuclein knockout mice have been described to be resistant or less sensitive to mitochondrial toxins [297–301]. Interestingly, α-synuclein knockout mice were reported to have qualitative and quantitative mitochondrial lipid abnormalities with a decrease in cardiolipin content, which was associated with a reduction in complex I/III activity [302]. From a recent yeast study it emerged that mitochondria play an important role in mediating the toxic effects of α-synuclein [303]. Buttner et al. showed that expression of wildtype or A53T mutant α-synuclein in chronologically aged yeast cells accelerates apoptosis and ROS production, which did not occur in strains lacking mitochondrial DNA.

All in all, increased α-synuclein expression as well as α-synuclein deficiency seems to be associated with mitochondrial abnormalities. However, at present it is difficult to reconcile the manifold observations in a unifying theory about a role of α-synuclein in mitochondrial function.

2.1.5. LRRK2

Mutations in the LRRK2 gene are the most common cause of genetic PD; they are responsible for the majority of autosomal dominant PD typically associated with late-onset and are also found in some cases which would have been classified as sporadic PD [304,305]. The LRRK2 gene encodes a large multidomain protein of 2527 amino acids, including a kinase domain related to the mixed lineage kinase family, a Roc domain (Ras in complex proteins) with similarity to the Ras/GTPase superfamily, a COR domain (C-terminal of Roc), a WD40-repeat domain and leucine-rich repeats (rev. in refs. [306–308]). Some pathogenic mutations seem to increase the kinase activity of LRRK2 in vitro, assessed by autophosphorylation or phosphorylation of generic substrates, which may suggest a toxic gain of function mechanism [309–312]. So far, our knowledge about the physiological function and the pathological mechanism of LRRK2 is limited. LRRK2 can bind to the outer mitochondrial membrane in mammalian brain and about 10% of overexpressed LRKK2 was found in association with the

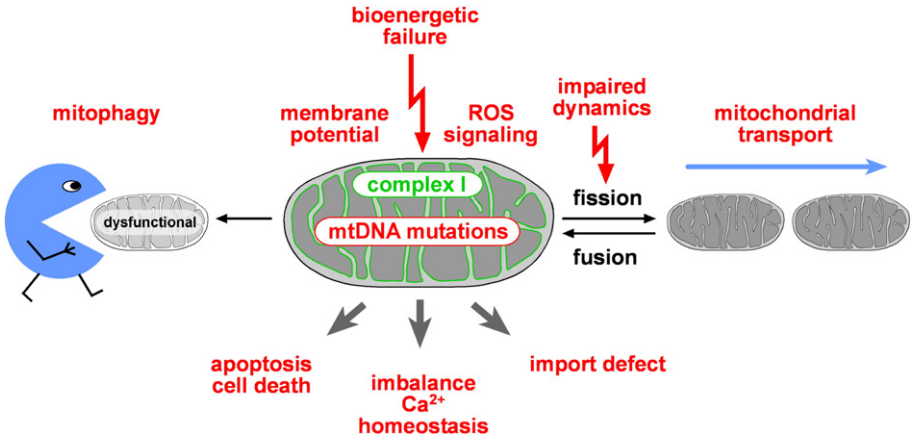

Fig. 2. Mitochondrial alterations associated with PD.

outer mitochondrial membrane [309,312,313]. However, it remains to be determined whether LRRK2 has an impact on mitochondrial integrity.

3. Perspective

Recent research on the function and dysfunction of PD-associated genes has provided fundamental new insights into biochemical pathways which are associated with the disease process. Moreover, these findings established that mitochondrial dysfunction is a common denominator of sporadic and familial PD, moving mitochondria to the forefront of PD research. Manifold facets of mitochondrial biology seem to be affected in PD (Fig. 2). Still, there will be tremendous work ahead of us to fit together the pieces of the puzzle into a conclusive concept. Likewise, the chronological order of the events implicated in mitochondrial damage and neuronal degeneration is far from being understood.

Considering the important role of mitochondria in energy metabolism, calcium homeostasis, cellular quality control pathways and cell death regulation, it is tempting to speculate that mitochondrial dysfunction contributes to the high vulnerability of dopaminergic neurons. These neurons are characterized by a high oxidative burden resulting from dopamine metabolism and excitotoxicity, while their antioxidative repertoire is rather limited (rev. in refs. [18,82]). In this context it is interesting to note that regiospecific differences in biochemical and structural parameters of brain mitochondria have been documented. Another key player seems to be calcium. Adult dopaminergic neurons are uniquely dependent on voltage-dependent L-type Ca^{2+} channels for autonomous pacemaking activity [314–317]. In keeping with a crucial role of mitochondria in regulating calcium homeostasis, a dysbalance in calcium buffering seems to be causally related to the selective degeneration of dopaminergic neurons (rev. in refs. [318]).

Collectively, the exceptional physiological features of dopaminergic neurons help to explain why mitochondrial fidelity and an effective cellular quality control and stress response management are paramount to the survival of these neurons, particularly in an aging individual. There is compelling evidence that at least some of the PD-associated genes interface with these pathways . It will now be a challenging endeavour to exploit these pathways as a rationale to halt or delay disease progression and to move basic research into clinical practice.

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